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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,054	02/06/2001	Peter Joseph Cassidy	080056-00020	3789

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EXAMINER	
GROSS, CHRISTOPHER M	
ART UNIT	PAPER NUMBER
1639	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/647,054	CASSIDY ET AL.	
	Examiner	Art Unit	
	Christopher M. Gross	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *29 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *113-144* is/are pending in the application.

4a) Of the above claim(s) *114-118,122,123,125,127-133,136,139 and 141-144* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *113,119-121,124,126,134,135,137,138 and 140* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/18/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Responsive to communications entered 9/29/2006. Claims 113-144 are pending. Claims 114-118,122-123,125,127-133,136,139,141-144 are withdrawn. Claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138 and 140 are under consideration.

Amended claim 126 has been considered.

Election/Restrictions

Over the course prosecution, if the elected species is found free of the prior art, the search will be extended to include withdrawn claims 114-118,122-123,125,127-133,136,139,141-144, in accordance with Markush Practice (see MPEP 803.02).

Priority

This application is a 371 of PCT/AU99/00207 03/24/1999 which claims priority to AUSTRALIA patent PP2548 03/24/1998. The acceptance notice from DO/EO mailed 11/1/2006 is in the file.

Maintained Claim Rejection - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 113, 119, 120, 121, 124, 126,134,135, 137, 138 and 140 are rejected under 35 U.S.C. 102(b) as being anticipated by Ma et al (1995 Protein Peptide Letters 2:347-350).

Response to Arguments

The declaration under 37 CFR 1.132 filed 9/29/2006 is insufficient to overcome the rejection of claims 113, 119, 120, 121, 124, 126,134,135, 137, 138 and 140 based upon Ma et al under 35 USC 102 (b) as set forth in the last Office action because:

Applicant argues, see applicant's arguments p 8-9 (9/29/2006), that Ma et al does not represent an enabling disclosure, and in accompanying said declaration under 37 CFR 1.132, applicant presents experimental data alleging that Ma et al has prepared an isomer, rather than the claimed 1,4 diazacycloheptane derivative, thus one of ordinary skill in the art would not be placed in possession of the claimed invention by following the procedure of Ma et al presented in scheme 2.

Specifically, applicant presents data indicating that the last Mitsunobo reaction shown in scheme 2 of Ma et al is ineffective under the conditions presented by Ma et al (i.e. Bzl Nitrogen protection; Ph_3P;DEAD in THF) to provide the claimed 1,4 diazacycloheptane derivative. It is noted, however that Ma et al perform the reaction at 20 degrees C for 60 hours, whereas applicant performed the reaction for only 48 hrs at a temperature not indicated. Thus, Applicants have not provided adequate proof to show that the reaction conditions set forth in Ma et al. will not work. Moreover, reactions that generally work can fail in peculiar situations where unfavorable steric and/or electronic interactions occur. Thus, the success or failure of a single reaction will not suffice to characterize the entire group.

Ma et al also present in scheme 1 as an alternative pathway for preparing said 1,4 diazacycloheptane derivatives which *does not employ* Mitsunobo chemistry (see also pg 348 first line "Two strategies have been studied"), however applicant has not

presented data to refute this pathway in said declaration or elsewhere in the application. Thus, Applicants' arguments and evidence are not commensurate in scope with the teachings of Ma.

In addition, "Possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention **with his [or her] own knowledge to make the claimed invention.**" In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). Emphasis added. Here, applicant has not presented an exhaustive study of Mitsunobo reaction conditions and/or nitrogen protecting groups to demonstrate that the amount of experimentation is undue. As evidenced Tsunoda et al (1996 Tetrahedron Lett. 37:2487-2458), alternative reaction conditions include Tosyl protection of Nitrogen and cyanomethylenetribuytlphosphorane (CMBP) in lieu of DEAD, both of which were available to one of ordinary skill in the art prior to the time the invention was made. The Examiner submits that trying alternative Mitsunobo reaction conditions does not constitute undue experimentation.

In conclusion, Ma et al represents an enabling disclosure, placing one of ordinary skill in the art in possession of the claimed 1,4-diazacycloheptane derivatives since, absent evidence to the contrary, the amount of experimentation to prepare the 1,4-diazacycloheptane derivatives is not undue, either through alternative Mitsunobo reaction conditions or else through following scheme 1 according to Ma et al.

Maintained Claim Rejections 35 USC § 103

Claims 113, 119, 120, 121, 124, 126,134,135, 137, 138 and 140 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gardner et al (1993 Tetrahedron

49:3433-3448 – IDS entry 9/25/2000) in view of Alkorta et al (1996 J. Molecular Modeling 2:16-25).

Response to Arguments

Applicant argues, see p 9-10 (9/29/2006) that not all elements are taught and that Alkorta teaches away from the claimed invention.

Applicants arguments have been considered, but are not persuasive for the following reasons.

In regard to not elements being taught by Gardner et al, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In regard to Alkorta et al teaching away from the claimed invention, a known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). The examiner submits that just because compounds 7 and 11 of Alkorta et al gave better similarity scores for an ideal gamma turn than compound 6 (the 1,4 diazacycloheptane derivative), Alkota et al does not disparage compound 6, in fact, Alkorta et al state on page 22, 3rd paragraph that seven member rings have good similarity to both types of gamma turns: classic and inverse.

Furthermore, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure

does not criticize, discredit, or otherwise discourage the solution claimed...." In re Fulton,391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

Finally, according to MPEP 2144.08 II A.4(a), a genus may be so small that, when considered in light of the totality of the circumstances, it would anticipate the claimed species or subgenus. For example, it has been held that a prior art genus containing only 20 compounds and a limited number of variations in the generic chemical formula inherently anticipated a claimed species within the genus because "one skilled in [the] art would... envisage *each member*" of the genus. In re Petering, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962) (emphasis in original). Since Alkorta et al teach only 14 gamma turn mimetics, which when combined with the primary sequence of Gardner et al, one of skill in the could readily envisage each gamma turn analog.

Interview

Applicant's request for an interview to discuss the above rejection under 35 USC 102 over Ma et al is hereby **granted**. Please call the Examiner to arrange a mutually agreeable time. See contact information below.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Gross whose telephone number is (571)272-4446. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz can be reached on 571 272-0763. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christopher M Gross
Examiner
Art Unit 1639

cg

JON EPPERSON
PRIMARY EXAMINER

S/N 09/647,054 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Peter Joseph Cassidy, et al.	Examiner: Christopher M. Gross
Serial No.:	09/647,054	Group Art Unit: 1639
Filed:	March 24, 1998	Docket No.: 707.025US1
Title:	PEPTIDE TURN MIMETICS	

DECLARATION UNDER 37 C.F.R. §1.132

I, Peter Joseph Cassidy, declare and say as follows:

1. I, Peter Joseph Cassidy, received my bachelor's degree with first class honors in 1989 and doctorate degree in 1999 from the University of Queensland, Brisbane, Australia. I am currently a Research Officer at the Institute of Molecular Bioscience of that university and Chief Scientific Officer of Mimetica Pty Ltd. I have authored or co-authored 2 scientific publications, and regularly present work at international symposia (eg Natural Peptides to Drugs April 2006, European Peptide Symposium September 2006). I have over 12 years experience working directly on or supervising work on peptide turn mimetics.

2. I am a named co-inventor of the subject matter claimed in the above-identified patent application and have reviewed the Office Action mailed Apr. 5, 2006 and am familiar with the prosecution history of this application, including the Response filed herewith. I hereby make this Declaration in support of the patentability of the claims of the application.

3. The Examiner has rejected claims 113, 119, 120, 121, 124, 126, 134, 135, 137, 138, and 140 on the basis of 35 U.S.C. §102(b) as being anticipated by Ma et al., 1995, Protein Peptide Letters, 2:347-350.

4. Provided herein is a summary of research investigations aimed at duplicating the research of Ma et al as described in the above-cited publication. I participated in or

CONSIDERED
12/29/06

supervised the collection of these data. These data are submitted to rebut the Examiner's assertion of anticipation of the enumerated claims on the basis of the Ma publication.

5. As outlined in the attached experimental procedures and results shown in the Appendix, I believe based upon convincing evidence that Ma misstated the structure of the reaction product of the final step in the Ma synthesis, the Mitsunobu cyclization that purports to yield the final product **1** from the acyclic precursor **11**. By carrying out the literature reaction, and carefully analyzing spectroscopic data in light of accepted scientific criteria, we have arrived at the conclusion that Ma did not in fact obtain structure **1**, but rather an isomer thereof. Thus, the Ma publication does not describe or enable a successful method for the preparation of a compound of structure **1**, and therefore Ma does not provide a synthetic route to the compound of structure **1**.

6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code, and that such willful false statement may jeopardize the validity of this application or any patent issuing therefrom.

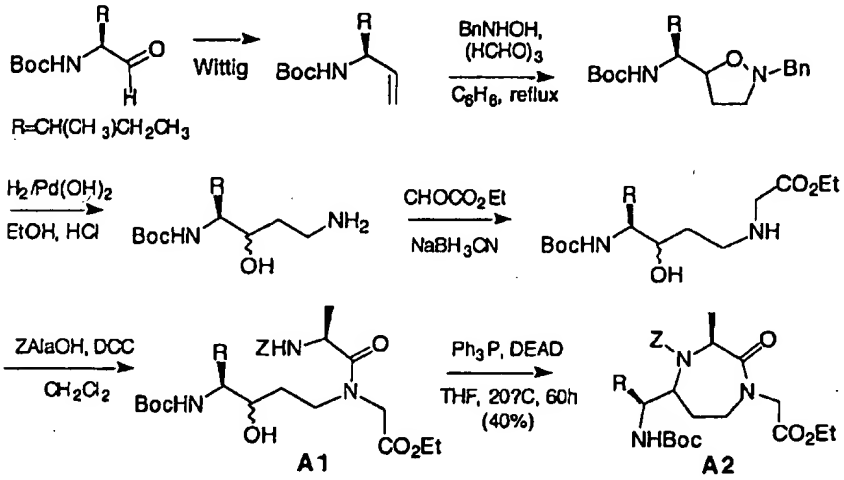
19 September 2006
Date

Peter Joseph Cassidy

APPENDIX

Attempted Repetition of the Synthesis of Ma *et al.*

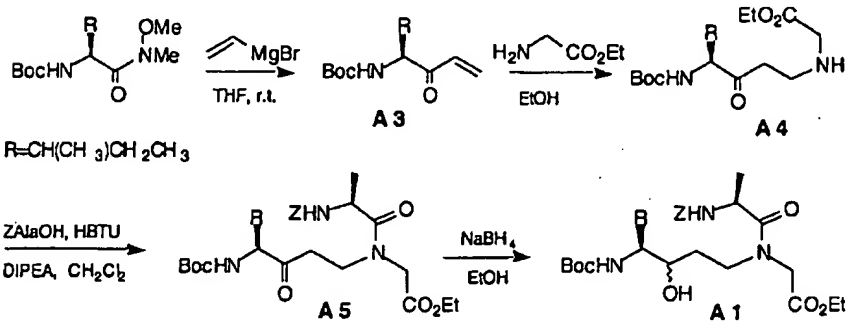
We have repeated the cyclization reaction described by Ma *et al.*, 1995, *Peptide and Protein Letters*, **2**, 347-350, and confirmed by NMR analysis and chemical transformation that the actual product is a structural isomer, not the γ-turn mimetic claimed. The synthesis and analyses and other material in support of the assertion that the method of Ma *et al.* does not represent a reduction to practice are presented below.



Scheme A1 Synthesis proposed by Ma *et al.* for a 1,4-diazepine γ-turn mimetic.

The key step in the proposed synthesis of Ma *et al.* is the cyclization of **A1** (identified as compound **11** in the Ma paper) to the protected target **A2** (identified as compound **1** in the Ma paper) using the Mitsunobu reagents, namely Ph_3P / DEAD. We repeated the synthesis of the cyclization precursor by our own methods as described below.

The alcohol **A1** was more conveniently prepared by the conjugate addition method described earlier than as illustrated in Scheme A1 (4 steps vs. 6 steps). The procedure used is summarized in Scheme A2.



Scheme A2

Thus, the Weinreb amide of Boc isoleucine was reacted with vinyl Grignard in THF to give the α-β unsaturated ketone **A3** by the following procedure: Boc-isoleucine-N-methoxy-N-methylamide (2.25 g, 8.2 mmol) was dissolved in anhydrous THF (20 mL) and cooled to 0 °C under nitrogen. To the stirred solution was added vinyl magnesium bromide in THF (20 mL of a ~1M solution) over 5 min. The reaction was very slow at 0 °C (negligible progress over 1 h), but much faster at room temperature (~70% product after 20 min). After stirring at room temperature for 90 min the reaction was poured into crushed ice/1M HCl and extracted with ether. The organic layer was washed with 0.5M HCl, water, aq. $NaHCO_3$ then brine and then dried over $MgSO_4$. The crude product was formed in good yield and purity and was used directly for the next reaction. TLC 25%EA/light pet. Rf=0.64. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.50, 1H, dd, J = 10, 17 Hz; 6.37, 1H, dd, J = 1, 17 Hz; 5.85, 1H, d, J = 10 Hz; 5.23, 1H, bd, J = 7 Hz; 4.58, 1H, dd, J = 4, 8 Hz; 1.88, 1H, m; 1.45, 9H, s; 1.32, 1H, m; 1.10, 1H, m; 0.98, 3H, d, J = 7 Hz;

0.90, 3H, d, J = 7 Hz. ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.0; 155.7; 134.0; 129.6; 79.60; 61.71; 37.50; 28.28 (Boc); 24.09; 16.04; 11.61.

Reaction of **A3** with glycine ethyl ester in ethanol to give **A4** by the following procedure: Glycine ethyl ester hydrochloride (1.0 g, 7.1 mmol) was reacted with **A3** (1.1 g, ~4.7 mmol) and DIEA (450 mg, 3.5 mmol) in ethanol (20 mL) at room temperature overnight. The reaction was diluted with ether (100 mL) and extracted in turn with aq. $NaHCO_3$ and water (x3). Petroleum ether was added (100 mL) and the solution extracted with 0.5M HCl:MeOH 4:1 (x3) (discard the organic layer). The acid washings were immediately neutralised with solid $NaHCO_3$ and then extracted with ethyl acetate and the ethyl acetate layer washed with water then brine and then dried over $MgSO_4$. Evaporation of the solvent *in vacuo* left 800 mg (~50%) of crude product of sufficient purity for use in the next reaction. TLC EtOAc Rf=0.52. ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.0; 171.7; 155.8; 79.57; 63.95; 60.76; 50.67; 43.69; 40.82; 36.74; 28.19 (Boc); 24.05; 16.01; 14.08; 11.51. Mass Spectrum (ISMS) m/z 345 (MH^+), calculated for $C_{17}H_{32}N_2O_5$: 344.

The amino ketone **A4** (690 mg, 2 mmol) was then coupled with Z-alanine to give **A5** using standard solution phase coupling procedure with HBTU reagent and DIEA in CH_2Cl_2/THF. The crude product was purified by flash chromatography eluting with 30% EtOAc in light petroleum for a yield of 94% (1.03 g). TLC EtOAc:light pet. 1:2 Rf=0.25. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34, 5H, m; 5.68, 1H, bm; 5.18-5.02, 3H, m's; 4.72, 0.5H, m; 4.48-4.07, 5H, m's; 3.88-3.54, 2.5H, m's; 2.75-2.05, 2H, m's; 1.89, 1H bs; 1.44, 1.43: 9H, 2s, Boc; 1.38, 1.5H, d, J = 6.9 Hz (alaHβ, one rotamer); 1.34-1.28, 5.5H, m's; 1.07, 1H, m; 1.00-0.82, 6H, m's. ^{13}C NMR (75 MHz, $CDCl_3$), signals due to the equivalent carbon in different rotamers are grouped in parentheses where possible: δ (209.0, 207.9); (173.39, 173.25); (169.15, 168.84); 155.75, 155.67, 155.56, 155.33: carbamate signals; 136.20; 128.31; 127.91; 127.80; (79.72, 79.57); 66.60; (64.01,

63.85); (61.61, 61.09); (50.96, 48.65); (46.63, 46.57); (43.75, 43.23); (40.02, 39.07); (36.56, 36.29); 28.14 (Boc); (24.09, 24.03); 18.74; 15.92; 13.85; (11.44, 11.38). Mass Spectrum (ISMS) m/z 550 (MH^+), calculated for $C_{28}H_{43}N_3O_8$: 549

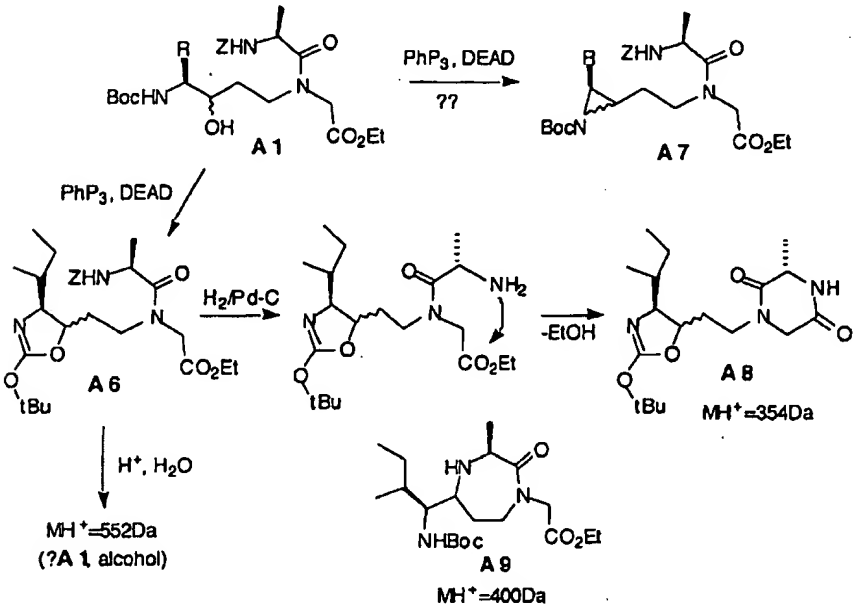
The ketone **A5** (430 mg, 0.78 mmol) was dissolved in ethanol (5 mL) and $NaBH_4$ (15 mg, 0.40 mmol) added to the stirred solution at room temperature, and stirring continued for 1 h. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate and washed with 1M HCl, water, aq. $NaHCO_3$, brine and then dried over $MgSO_4$. The residue after solvent evaporation was purified by flash chromatography eluting with ethyl acetate:light petroleum ~1:1 (some separation of diastereomers occurred) for an approximately quantitative yield of the alcohol **A1**. TLC EtOAc:light pet. 1:1 Rf=0.28. **^{1}H NMR** (300 MHz, $CDCl_3$), late eluting fractions, rotamers/diastereomers >2:1: δ 7.39-7.29, 5H, m; 5.80, 1H, d, J=9 Hz; 5.15, 1H, d, J=12 Hz; 5.11-5.49, ~1H, m; 4.96, ~1H, d, J=12 Hz; 4.67-4.42, ~1H, m's; 4.19, ~2H, bq, J=7.2 Hz; 4.03-3.88, ~2H, bm; 3.88-3.40, ~4H, m's; 3.30-3.09, 1H, m; 1.96-1.66, ~2H, m; 1.55, ~1H, m; 1.42, 9H, s, (Boc); 1.331.33, d, J=7 Hz; 1.28, t, J=7.2 Hz; 1.15, d (minor isomer), J=6.8 Hz; 1.37-1.05 ~8H; 1.0-0.82, ~6H, m's. **^{13}C NMR** (75 MHz, $CDCl_3$), major peak only shown unless otherwise indicated: δ 174.0; 169.0; 156.4; 156.3; 135.9; 128.4; 128.1; (128.0, minor isomer); 127.9; 78.92; 66.96; (66.56, minor isomer); 66.11; 61.26; 59.49; 47.74; 46.10; 45.24; 34.38; 31.31; 28.30 (Boc); 22.29; 18.85; 16.41; 14.00; 11.90. Mass Spectrum (ISMS) m/z 552 ($M+H^+$), calculated for $C_{28}H_{45}N_3O_8$: 551

The alcohol **A1** was reacted with the Mitsunobu reagents as described by Ma *et al.* (Scheme 4.37) as follows: The alcohol **A1** (150 mg, early eluting fraction) was dissolved in dry THF and triphenylphosphine (71 mg) added. To the stirred solution at room temperature under nitrogen was added DEAD (43 uL), and stirring continued for 24 h. Analysis of the crude reaction revealed the formation of a dehydration product ($M+H^+$=534 Da) in moderate yield. Another equivalent of triphenylphosphine/DEAD

was added and stirring continued for a further 48 h. The solvent was removed *in vacuo* and the residual oil dissolved in ether/petroleum ether and left to stand to encourage the precipitation of the triphenylphosphine oxide and diethoxycarbonyl hydrazine (white solid, filtered off). The oil remaining after evaporation of the filtrate was purified by flash chromatography eluting with petroleum ether and 10-100% ether in petroleum ether, yield was ~40% (60 mg). TLC ethyl ether Rf=0.61. The NMR spectra were quite complex, as may be expected from the possible mixture of diastereomers/ rotamers. However, it was possible to clearly identify the alanine spin system with Hα at 4.71ppm (1H, broad pentuplet, J~8Hz). 1D decoupling experiments were performed: irradiation at 4.7ppm caused the collapse of two signals to singlets, a doublet centred on 1.40ppm (J=7Hz, alanine Hβ), and a broad doublet (1H, J=8Hz) at 5.62ppm (alanine NH). These assignments were confirmed by irradiation at 1.4ppm which caused collapse of the multiplet at 4.71ppm to a doublet with J=8Hz. The presence of the NH proton in the alanine spin system rules out the γ-turn mimetic A2 proposed by Ma *et al.* as a possible structure for the product, and leaves open the possibility of A6 or A7 (Scheme A3) which we felt were more probable products, as the true structure. **^{1}H NMR** (300 MHz, $CDCl_3$): (selected peaks) δ 5.62, ~1H, bd, J=8 Hz; 4.71, ~1H, m(q); 1.40, d, J=6.8 Hz. Decoupling experiments: irradiate 1.4 ppm -> 4.71 = doublet, J=8 Hz; irradiate 4.71 ppm -> 1.4 = singlet, 5.62 = singlet. **^{13}C NMR** (75 MHz, $CDCl_3$): the spectra were difficult to analyse due to the presence of rotamers/diastereomers, peak broadening and impurities which co-eluted. There were a couple of notable features: (i) the appearance of a new peak at the relatively unusual shift of 160.7 ppm possibly due to the carbamate derived oxazoline carbon (only one carbamate resonance was observed, 155.5 ppm), and (ii) the downfield shift of the tertiary Boc carbon resonance which was observed at 81.22 ppm, whereas NHBoc tertiary carbon shifts are normally at a shift upfield of 80 ppm (e.g.

78.9 in the alcohol precursor). Mass Spectrum (ISMS) m/z 534 (MH^+), calculated for $C_{28}H_{43}N_3O_7$: 533

To confirm the results of the NMR analysis a further experiment was carried out. The product material was hydrogenated (EtOH, Pd-C) to remove the Z group. If the product has structure **A6** or **A7** then the amine will now be free to form the diketopiperazine **A8**, a facile reaction in such a system, Scheme A3. If any of the target γ-turn mimetic **A2** is present then it will be deprotected to the (very stable) free amine **A9** and be easily detected in the ionspray mass spectrum (ISMS). Analysis of the product mixture from the hydrogenation revealed the presence of a mass peak corresponding to the diketopiperazine (MH^+=354Da), but no trace whatsoever of **A9** (MH^+=400Da).

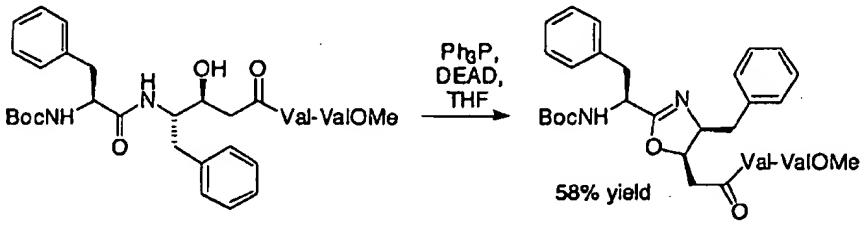


Scheme A3

Finally, it was also observed that the cyclization product (which we propose to be **A6**) was easily hydrolysed by dilute aqueous acid (e.g. room temperature 0.1% aq. TFA, 12h), back to the alcohol **A1** (or a compound of the same mass). This last observation is

more consistent with the product structure being the oxazoline **A6** rather than the aziridine **A7** as the oxazoline is more probably subject to facile hydrolysis by aqueous acid, the facile hydrolysis is entirely inconsistent with the structure **A2** proposed by Ma *et al.*

In further support of **A6** as the product structure, peptide alcohols similar in structure to **A1** have been reported to form oxazolines (Galéotti, Montagne *et al.* 1992), for example:



Other evidence against formation of **A2** by the Mitsunobu reaction as proposed by Ma *et al.* is presented below:

(1) Difficulty of forming seven membered rings via the Mitsunobu reaction

(a) Literature precedent

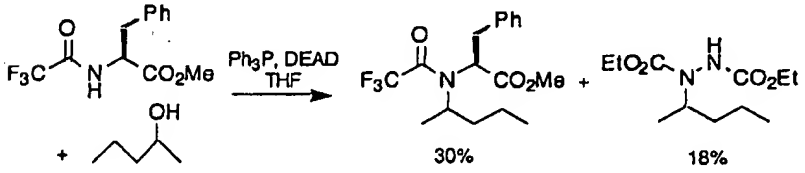
The literature on the formation of cyclic amines and amides with the Mitsunobu reaction contains numerous examples of the formation of 3-6 membered rings (Carlock and Mack 1978; Robinson, Barry *et al.* 1983; Pfister 1984; Kelly, Eskew *et al.* 1986; Henry, Marcin *et al.* 1989; Bernotas and Cube 1991), but very few cases of seven membered ring formation. In one paper on the cyclization of amino alcohols the faliure to form a simple seven membered target is specifically described.(Bernotas and Cube 1991) In the organic reactions entry on the Mitsunobu reaction (Hughes 1992) three instances of seven membered ring formation with carbon-nitrogen bond formation are

described: all three involve a primary alcohol, two occur in polycyclic systems and appear to be special cases, and the third involves alkylation of a hydroxamide - far easier than an amide due to higher NH acidity.

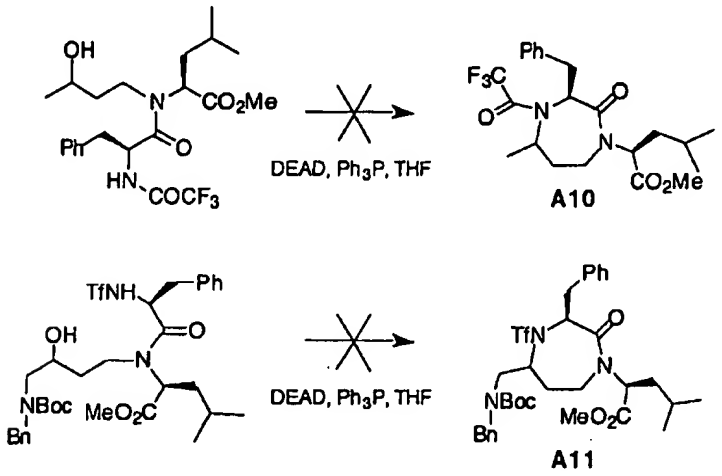
There appears to be no literature precedent for the formation of a seven membered ring to a simple amide or carbamate nitrogen. In addition there is little precedent for secondary amide N-alkylation with hindered secondary alcohols, as is proposed to occur in the formation of **A2**.

(b) Synthetic studies

Extensive studies on the use of the Mitsunobu reaction for the formation of the target system were carried out in our laboratories prior to becoming aware of the proposed synthesis. In our hands this approach was ineffective. The key reactions are described in Schemes A4 and A5.



Scheme A4

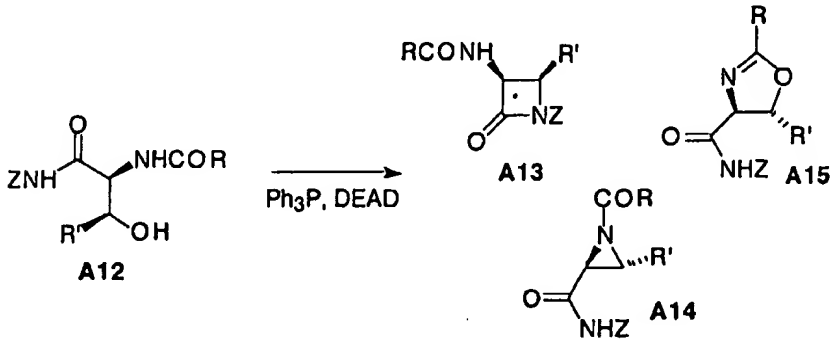


Scheme A5

The formation of the alkylation product was somewhat successful in the intermolecular reaction (Scheme A4), but this success was not repeated in cyclic systems (Scheme A5). No significant amount of the target cyclic products **A10** or **A11** was detected.

(2) Competing reactions - oxazoline and aziridine formation.

Cyclization of β-hydroxy amide derivatives A12 with the aim of forming β-lactams **A13** also results in the formation of the aziridine **A14** and oxazoline **A15** products shown in Scheme A6.(Hughes 1992) Another example of oxazoline formation was described above.(Galéotti, Montagne *et al.* 1992)



Scheme A6

As the Mitsunobu reaction is relatively effective for the formation of small ring sizes, it is quite probable that the formation of aziridines and oxazolines will compete with other possible cyclization s, other factors being equal. Such competition can take place in the proposed synthesis, the products would then be **A6** and/or **A7**, Scheme A3. Both the aziridine and oxazoline are isomeric with the target compound **A2**, possibly leading to their confusion with the target, a situation easily resolved by ^{1}H NMR as we demonstrated above.

We also note that there was a publication after the filing date of the present application from the same laboratory, namely the *"Laboratoire des Aminoacides, Peptides et Protéines, UMR 5810 CNRS-Universités Montpellier I et II.* Nouvet et al., *Tetrahedron* 1999, **55**, 4685-4698. This document shares a common author with the earlier Ma paper, namely René Larzaro. The applicants respectfully point out for the Examiner's attention that this publication in fact contradicts the Ma publication. The paper describes the synthesis of the γ-turn mimetics using a sulphonamide group in place of the Z (benzyloxycarbonyl) group in cyclization akin to the cyclization allegedly carried out by Ma. Importantly for the purposes of the disclosure in Ma this document specifically notes on page 4687, lines 3 to 4, that the *"sulfonamide group was found to be*

essential for the cyclization step : other tested N-substituents (-Z, -Troc, or -Ac, unpublished results) were inefficient whatever the redox system was used". This paper by Nouvet further supports the contention that the Z group as used in the earlier Ma paper would not in fact work for cyclizations of this type.

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